5. (Original) The method of claim 4, wherein said noribogaine is administered at a dose of between 1.0 mg and 30 mg per kg of body weight.

6. (Original) A method of treating a patient to alleviate pain, comprising:

a) administering systemically to said patient an amount of noribogaine; and

b) concomitantly administering systemically to said patient an amount of one or more opioid antagonists; wherein said respective amounts of noribogaine and said one or more opioid antagonists are effective to reduce or eliminate pain in said patient.

7. (Original) The method of claim 6, wherein said opioid antagonist is naloxone, administered to said patient at a dose between 0.05 mg and 0.5 mg for each mg of noribogaine.

8. (Original) The method of claim 6, wherein said opioid antagonist is naltrexone, administered to said patient at a dose of between 0.05 mg and 0.5 mg for each mg of noribogaine.

9. (Original) The method of claim 6, wherein said noribogaine and said opioid antagonist are administered transdermally.

Remarks

After amendment, claims 1-9 remain pending in the present application, claims 10-24 having been cancelled *without prejudice* pursuant to the Examiner's restriction requirement and Applican's decision to elect with traverse to prosecute the invention of claims 1-9. Upon the indication of allowable subject matter, and before the issuance of any patent from this application, Applicant will give consideration to filing a divisional application for the claimed subject matter cancelled in this paper. The specification has been amended previously to reflect Applicant's claim of priority from the original PCT application PCT/US98/18284, as well as provisional application serial number 60/057,921. No new matter has been added by the present amendment.

The Examiner has rejected claims 1-9 under 35 U.S.C. §103 as being obvious over Epstein, et al., U.S. No. 3,715,361 ("Epstein") and GB 841,697 ("GB '697"), in view of

Bagal, et al., ("Bagal") and Hussain, U.S. No. 4,464,378 ("Hussain"). The Examiner essentially argues that despite Applicant's arguments previously submitted, this was unconvincing because Applicant did not consider the teachings of a combination of references. The Examiner relies on Epstein for putatively disclosing that ibogaine and its derivatives are analgesic agents and consequently, the agents are therefore useful in treating or alleviating pain. The Examiner relies on GB '697 for teaching that ibogaine is an analgesic agent and therefore is useful in an analgesic composition for treating or alleviating pain. The Examiner acknowledges that the prior art does not expressly disclose the employment of noribogaine alone or in combination with an opioid antagonist in a method of treating a patient to alleviate pain. The Examiner cites Bagal for disclosing that noribogaine is a known active metabolite of ibogaine and that noribogaine enhanced morphine antinociception was more pronounced than with comparable ibogaine treatment. Finally, the Examiner cites Hussain for teacing that opioid antagonists such as naloxone, naltrexone and nalorphine are well known analgesics and therefore useful in a method of treating or alleviating pain in a patient.

Given the teachings of the prior art, the Examiner contends that one of ordinary skill would have been motivated to employ noribogaine alone or in combination with an opioid antagonist such as naloxone, naltrexone or nalorphine in a method of treating a patient to alleviate pain and to optimize the effective amounts of agents in the composition herein to be administered. In particular, the Examiner cites and relies heavily on Bagal for teaching the instant invention for the reasons which are set forth in the office action on page 3. Applicant respectfully traverses the Examiner's rejection.

The present invention relates to the unexpected discovery that noribogaine, in contrast to ibogaine, may be used as a non-addictive analgesic agent, *alone* or in combination with an opioid *antagonist* as a particularly effective non-addictive analgesic. Without being limited by way of theory, it is believed that noribogaine functions, at least in part, as a full *mu* (μ) opiod receptor *agonist* without addictive properties. Consequently, the present invention makes use of noribogaine's unique activity and represents a particularly effective method for alleviating pain, an advance in the art and an exciting improvement over the treatments of the prior art. Methods which make use of noribogaine in combination with an opioid antagonist represent alternative embodiments of the present invention. Note that noribogaine is particularly effective as an analgesic agent because it is a full *mu* opioid agonist, is particularly effective in

this regard, and is also *non-addicitve*, in contrast to the opioid analgesics, i.e., the opioid agonists. In addition, in contrast to ibogaine, noribogaine is vastly superior in analgesic activity and is free from the psychomimetic side effects of ibogaine.

In contrast to the Examiner's arguments, the present invention is clearly patentable and non-obvious over the teachings relied upon by the Examiner. The Examiner cites Epstein and GB '697, in view of Bagal and Hussain as rendering the present invention obvious. It is respectfully submitted by Applicant that Epstein and GB '697 do not teach or suggest the present invention, that Hussain, by failing to even mention the present invention, does not obviate the deficiencies of Epstein and GB '697, and if one goes further and asserts Bagal against the present invention, the combination of references actually *teaches away* from the present invention. A detailed discussion of the patentability of the present invention follows.

It is clear from the art and even the Examiner's office action that none of the references teach noribogaine as an analgesic, alone or in combination with an opioid *antagonist* as claimed. A review of Epstein shows that this reference does not even disclose noribogaine. Note that Epstein discloses a series of acyl derivatives of 10-methoxyibogamine analogs for use as potential analgesic/anti-inflammatory analogs. Epstein does not disclose noribogaine, which is presented in the present specification on page 6. Epstein does not disclose ibogaine as an analgesic agent (indeed, it is not known in the art as an analgesic agent), but rather points to derivatives of ibogaine as having analgesic and anti-inflammatory activity. Moreover, the mere assertion of activity does not evidence that the compounds would necessarily be used as pharmaceutical agents. In addition, in the chemical compounds which are disclosed by Epstein at columns 1 or 2 or otherwise described in Epstein, noribogaine is not discussed or suggested. In each analog which is disclosed by Epstein, the O-methyl group on the benzene ring of the molecule is always an O-methyl group. Epstein completely failed to appreciate the potential activity of noribogaine or that the O-methyl group is advantageously converted to a hydroxyl group to provide the activity of noribogaine. Because Epstein does not disclose noribogaine or the chemical conversion of the O-methyl group which may be advantageously employed in noribogaine to provide its activity, Epstein clearly does not disclose or suggest the present invention. There is no disclosure in Epstein that ibogaine is a particularly useful stand-alone analgesic agent itself- indeed the entire rationale behind the approach of Epstein is to find a useful analgesic because ibogaine is not.

GB '697 describes the use of a number of narcotic morphine analogs (including morphine) in combination with ibogaine or tabernanthine for analgesic use. GB '697 does not disclose noribogaine as an analgesic agent alone, and further suggests the use of an addictive analgesic agent having morphine-like characteristics in combination with ibogaine or tabernanthine. This disclosure is actually duplicative in some measure with Bagal, discussed infra. In preferred embodiments of GB '697, as set forth in examples 1-2 5, 7-8 and 11, the use of morphine is described in combination with ibogaine or tabernanthine. This teaching is in complete contrast to the present invention inasmuch as the present invention relies on noribogaine as a *nonaddictive* analgesic acting *alone* in the first instance, and when combined with another agent, that agent is an opioid antagonist- i.e., an *opioid inhibitor*, not an *agonist* such as morphine. Thus, GB '697 clearly does not teach the present invention for it fails to teach or suggest noribogaine even obliquely, and when it discloses ibogaine, ibogaine is disclosed *in combination* with another agent, that agent being the addictive analgesic agent morphine. ***Note that GB '695 clearly indicates at page 2, column 1, lines 5-6 that the art recognized that ibogaine per se did not have analgesic activity.*** GB '697 clearly does not obviate the deficiencies of Epstein in failing to disclose or suggest the present invention.

Turning to Hussain, this reference completely fails to even disclose or suggest noribogaine and consequently, fails to disclose or suggest the present invention. In the present invention, the use of noribogaine *alone or in combination* with an opioid antagonist is claimed. The use of an opioid antagonist *only* in combination with noribogaine is claimed. None of Epstein, GB '697 or Hussain teaches that noribogaine may be used as an analgesic, alone or in combination with an opioid antagonist. Hussain in particular merely provides certain known compounds adapted for nasal administration. However, note that the art does not recognize that opioid antagonists have analgesic activity, and it is respectfully submitted that oioid antagonists do not exhibit any significant analgesic activity. Moreover, Hussain does not even mention noribogaine or ibogaine. Consequently, none of these references alone or in combination teaches or suggests the present invention and the present invention is non-obvious over the disclosure of these references.

Turning to Bagal, it is respectfully submitted that this reference does not disclose or suggest the present invention of using noribogaine *alone or in combination with an opioid*

antagonist as an effective analgesic agent. In the first instance, Bagal is prior art under 102(a), inasmuch as the Bagal paper published on November 25, 1996, a date which is less than a year after the provisional application from which the present application claims priority was filed.[1] Notwithstanding the question as to whether or not Bagal even is prior art, it is respectfully submitted that Bagal's teachings in combination with the other references do not render the present invention invalid. A review of the Bagal disclosure evidences that the teachings of this reference actually *teach away* from the present invention because this reference simply teaches that noribogaine, like ibogaine, may be used *in combination* with morphine. Bagal discloses the impact of ibogaine and noribogaine on other opiate actions. Bagal investigated the potentiation of ibogaine's effect on morphine analgesia. In particular, Bagal describes experiments which investigated the effects of ibogaine and noribogaine on morphine-induced antinociception. The experiments of Bagel clearly resulted in the finding that the co-administration of ibogaine and morphine resulted in an enhancement of morphine action which was dose dependent (see page 259 right column and 260, left column). Experiments involving noribogaine, which are described on pages 260-261, evidence that noribogaine exhibited *only slight antinociceptive properties alone* and minimal effects on *morphine* antinociception when given 19 hours earlier (Bagal, page 261, top right column), but significant antinociceptive activity when co-administered with morphine. Thus, the teachings of Bagal show that noribogaine, like ibogaine, may be have potentiated the analgesic effects of morphine within the test system employed.

In Bagal, contradictions to any conclusion of noribogaine's use as an analgesic come from:

1) Figure 1: Ibogaine has no effect on nociception when given alone- 19 hours prior. This is when noribogaine would likely be present- yet it has no effect; and

2) Figures 4 and 5: Looking at the plots of where noribogaine is given alone; although there is a trend toward an effect, it is deemed insignificant due to the similarity of both plots where noribogaine is given 19 hours prior and when noribogaine is given immediately.

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[1] Although it is Applicant's view that Bagal does not impact the present invention or otherwise render the present invention invalid, either alone or in combination, Applicant reserves the right to make the appropriate showing to remove Bagal as a reference against the present application.

Clearly, the slight slope provided has nothing to do with the drug.

Bagal concluded that noribogaine, when co-administered with morphine, simulated the results obtained with ibogaine-morphine co-administration. Thus, Bagal concluded that both ibogaine and noribogaine increased morphine antinicieption when *co-administered with morphine*. Bagal also concluded that a 19 hour pretreatment with noribogaine showed only a slight ("if any") enhancement of morphine antinociception (p. 261, right column, bottom). **Bagal concluded that noribogaine itself did not possess significant antinociceptive activity alone, but did possess significant antinociceptive effect only when combined with morphine**. Thus, Bagal *teaches* away from the present invention, which is directed to the use of noribogaine alone or in combination with an opioid **antagonist** to reduce or eliminate pain in a patient. In contrast, one of ordinary skill, reviewing Bagel, would conclude that, *at best,* the administration of noribogaine may be used in combination with morphine to provide significant antinociception activity, but that noribogaine *itself* was not a viable analgesic *itself.* Moreover, because the art recognized that opioid antagonists did not possess appreciable analgesic activity and morphine was an extremely potent opioid analgesic, a combination of noribogaine and an opioid antagonist is clearly not taught. In essence, the Bagal teaching completely contradicts the present invention.

Thus, Bagal does nothing to obviate the deficiencies of Epstein, GB '697 or Hussain. Indeed, if one of ordinary skill could draw any conclusions from Bagal, it is that noribogaine alone should not even work in the present invention, and that if noribogaine was to be used in an analgesic application, it only would be in combination with morphine, a potent opioid analgesic. However, that is clearly not the present invention. In contrast to the teachings of the art, Applicant has discovered that not only does noribogaine work alone (a concept which is clearly contravened by the conclusions reached by Bagal), but that noribogaine is also effective as an analgesic in combination with an opioid *antagonist*, a concept which is contravened by the putative requirement of Bagal that morphine, a potent opioid agonist is required.

Based upon the teachings of Bagal and the only reasonable conclusions to be taken from that reference by the routineer, Applicant respectfully submits that Bagal actually *teaches away* from the present invention, in the first instance by suggesting that noribogaine cannot be

used alone as an analgesic and in the second instance by suggesting that noribogaine can be effective when combined with morphine, a potent opioid agonist, not an opioid *antagonist* as is suggested by the present invention.

The Examiner contends that Applicant did not provide sufficient clarity with respect to the patentability of the present invention over the combination of references cited. However, Applicant respectfully submitted and reiterates that a combination of the teachings of the references cited against the instant application does not render the present invention obvious. Either the references are devoid of any teaching of noribogaine, or where noribogaine is disclosed, those references actually teach that the present invention is not a viable approach or should be used in combination with morphine (opioid analgesia), an approach the instant invention clearly *avoids*. Consequently, because the art is wholly deficient and completely fails to teach or suggest the present invention, Applicant respectfully submits that the present invention is patentable.

Notwithstanding the deficiencies of the art, the Examiner posits in the office action on page 3 that because Bagal discloses that noribogaine is an active metabolite, that disclosure can be used to support the view that the present invention is unpatentable. Applicant disagrees. What Bagal posits (and what the routineer may glean from Bagal) is that noribogaine may be at least partially responsible for the activity ibogaine exhibits in enhancing morphine antinociception. Thus, Bagal perhaps suggests that noribogaine may be used to substitute for ibogaine in being combined with morphine. Bagal, however, does not suggest noribogaine may be used *alone, or in combination with an opioid antagonist*. Notwithstanding the Examiner's arguments to the contrary, Bagal clearly states on page 261, in the second column, at lines 1-3, that "noribogaine had only slight antinociceptive properties and minimal effects on morphine antinociception." However, when combined with morphine, noribogaine had an effect, perhaps even better than ibogaine when combined with morphine. Thus, it is respectfully submitted, that Bagel clearly does not teach that noribogaine is useful as a "stand-alone" analgesic, but rather that noribogaine may be an effective agent *when combined with morphine, an opioid agonist*. A review of the amended claims evidences that Applicant has avoided any possible interpretation that claims read on that approach (a combination of noribogaine in combination with an opioid agonist).

Additionally, the Examiner has relied on the fact that because Bagal disclosed that noribogaine is an active metabolite of ibogaine, one of ordinary skill would recognize that noribogaine could be used in the same manner as ibogaine to alleviate pain. Indeed, Applicant concedes that Bagal teaches that noribogaine can be used to replace ibogaine in combination with an opioid analgesic such as morphine. However, there is no teaching or suggestion that because noribogaine is an active metabolite of ibogaine, it can be used *alone or in combination with an opioid antagonist* as claimed. It is noted here that ibogaine has not been posited for use as an analgesic agent *alone*, in the first instance because it has virtually no activity as an analgesic agent (see, GB '695, which clearly indicates at page 2, column 1, lines 5-6 that the art recognized that ibogaine *per se* did not have analgesic activity) and in the second instance because it exhibits substantial psychotrophic side effects, thus negating its use a stand-alone analgesic (assuming it had the requisite activity). Consequently, the fact that ibogaine is taught by Bagal for use in combination with an addictive opioid agonist such as morphine does not allow one of ordinary skill to make the inventive leap that noribogaine can be used *alone or in combination with an opioid antagonist* for the treatment of pain.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited. Applicants previously have cancelled 15 claims in the present application.

No fee is therefore due for the presentation of this amendment. A petition for a two month extension of time is enclosed as is a notice of appeal and the appropriate fee. If any fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838.

Respectfully submitted,
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